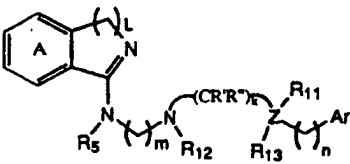


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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 403/14, A61K 31/505, C07D 209/44, A61K 31/40, C07D 401/14, A61K 31/495, C07D 403/12</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/29410</b> <b>(43) International Publication Date:</b> 9 July 1998 (09.07.98)
<b>(21) International Application Number:</b> PCT/US97/00967 <b>(22) International Filing Date:</b> 2 January 1997 (02.01.97) <b>(71) Applicant (for all designated States except US):</b> NEUROGEN CORPORATION [US/US]; 35 N.E. Industrial Road, Branford, CT 06405 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> HE, Xiao-shu [US/US]; Apartment #33, 1171 Main Street, Branford, CT 06405 (US). deCOSTA, Brian [GB/CA]; Apartment #605, 25 Belford Road, Toronto, Ontario M5R 2K1 (CA). WASLEY, Jan, W., F. [US/US]; 102 Colonial Drive, Madison, CT 06443 (US). <b>(74) Agents:</b> SARUSSI, Steven, J. et al.; McDonnell Boehnen Hulbert & Berghoff, 7th floor, 300 South Wacker Drive, Chicago, IL 60606 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> 1-(N'-(ARYLALKYLAMINOALKYL)) AMINOISOINDOLES; DOPAMINE RECEPTOR SUBTYPE SPECIFIC LIGANDS		
<div style="text-align: center;">  </div> <div style="text-align: right;">(1)</div>		
<b>(57) Abstract</b> <p>Disclosed are compounds of formula (1) or the pharmaceutically acceptable salts thereof wherein the 6-membered A ring may be optionally substituted with up to four groups independently selected from halogen, hydroxy, lower alkyl, or lower alkoxy; Ar represents optionally substituted aryl or heteroaryl; Z represents carbon or nitrogen provided that, where Z is carbon, R<sub>11</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy, or phenyl optionally substituted with one or two groups selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and where Z is nitrogen, R<sub>11</sub> represents an electron pair; R<sub>5</sub> is hydrogen or lower alkyl; L and m represent integers; n is 0, or an integer; R<sub>12</sub> and R<sub>13</sub> independently represent lower alkyl; or together may form an optionally substituted 5-11 membered ring with the nitrogen atoms to which they are bonded; CR'R'' represents a methylene group optionally substituted with lower alkyl; and k is an integer of from 1 to 3, which compounds are useful in treating various neuropsychological disorders including, for example, schizophrenia, dementia, depression, anxiety, Parkinson-like motor disorders and motion disorders related to the use of neuroleptic agents.</p>		

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**WO 98/29410**

**PCT/US97/00967**

**1-(N'-(ARYLALKYLAMINOALKYL)) AMINOISOINDOLES;  
DOPAMINE RECEPTOR SUBTYPE SPECIFIC LIGANDS**

5 **Field of the Invention**

This invention relates to aminoisoindole derivatives which selectively bind to brain dopamine receptor subtypes. More specifically, it relates to 1-(N'-(arylalkylaminoalkyl)) aminoisoindoles and to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating various neuropsychochological disorders.

10 **Description of the Related Art**

Schizophrenia or psychosis is a term used to describe a group of illnesses of unknown origin which affect approximately 2.5 million people in the United States. These disorders of the brain are characterized by a variety of symptoms which are classified as positive symptoms (disordered thought, hallucinations and delusions) and negative symptoms (social withdrawal and  
15 unresponsiveness). These disorders have an age of onset in adolescence or early adulthood and persist for many years. The disorders tend to become more severe during the patient's lifetime and can result in prolonged institutionalization. Within the United States of America, approximately 40% of all hospitalized psychiatric patients suffer from schizophrenia.

During the 1950's physicians demonstrated that they could successfully treat psychotic  
20 (schizophrenic) patients with medications called neuroleptics. This classification of antipsychotic medication was based largely on the activating (neuroleptic) properties of the nervous system by these drugs. Subsequently, neuroleptic agents were shown to increase the concentrations of dopamine metabolites in the brain. This finding suggested that altered neuronal firing of the dopamine system contributed in some way to the aberrant behavior observed in schizophrenic  
25 patients. Additional evidence indicated that dopamine could increase the activity of adenylate cyclase in the corpus striatum, an effect reversed by neuroleptic agents. Thus, cumulative evidence from these and later experiments strongly suggested that the neurotransmitter dopamine was involved in schizophrenia.

One of the major actions of antipsychotic medication is the blockade of dopamine receptors in brain. Several dopamine systems appear to exist in the brain and at least five classes of dopamine receptors appear to mediate the actions of this transmitter. These dopamine receptors differ in their pharmacological specificity and were originally classified on the basis of their ability to bind various dopaminergic ligands.

The butyrophenones are a class of drugs containing many potent antipsychotic drugs. Perhaps the most prominent member of this class of compounds is the antipsychotic drug haloperidol (chemical name). Haloperidol binds relatively weakly at the major dopamine receptor subtype which activates adenylate cyclase (commonly classified as the D<sub>1</sub> dopamine receptor). In contrast, haloperidol displayed binding affinity at a dopamine receptor subtype which suppressed the activity of adenylate cyclase (commonly classified as D<sub>2</sub> receptors) in the subnanomolar range.

Recently, three additional dopamine receptor subtypes have been identified using the often congruent sciences of receptor pharmacology and molecular biology. These new dopamine receptors have been labeled as D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub>. The D<sub>3</sub> and D<sub>4</sub> subtypes are pharmacologically related to the D<sub>2</sub> receptor via their ability to suppress the activity of adenylate cyclase. Conversely, the D<sub>5</sub> receptor is classified as a "D<sub>1</sub>-like" dopamine subtype through its ability to stimulate cyclase activity.

Recently, a new group of drugs (such as sulpiride and clozapine) have been developed with a lesser incidence of extrapyramidal side effects (EPS) than classical neuroleptics. In addition, there is some indication that they may be more beneficial in treating negative symptoms in some patients. Since all D<sub>2</sub> blockers do not possess a similar profile, hypotheses underlying the differences have been investigated. Major differences have been detected in the anticholinergic actions of these drugs. It has also been suggested that the dopamine receptors in motor areas may differ from those in the limbic areas which are thought to mediate the antipsychotic responses. The existence of the D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub> and other as yet undiscovered dopamine receptors may contribute to this profile. Some of the atypical compounds possess similar activity at D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors. The examples of this patent fall into this general class of molecules.

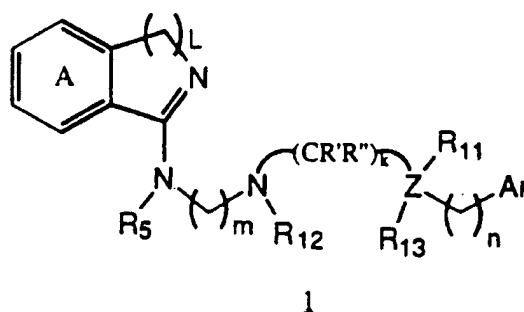
Using molecular biological techniques it has been possible to clone cDNAs coding for each of the pharmacologically defined receptors. There are at least two forms of D1 which have been identified as D<sub>1</sub> and D<sub>5</sub>, and two forms of D<sub>2</sub>, identified now as D<sub>2</sub> and D<sub>4</sub> dopamine receptors. In addition, there is at least one form of D<sub>3</sub> dopamine receptor. The 1-(N'-  
5 (arylalkylaminoalkyl))aminoisoindoles of this invention possess differential affinities for each receptor subtype.

### SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula 1 which interact with dopamine receptor subtypes.

The invention provides pharmaceutical compositions comprising compounds of Formula 1.

- 5 The invention also provides compounds useful in treating affective disorders such as schizophrenia and depression as well as certain movement disorders such as Parkinsonism. Furthermore, compounds of this invention are useful in treating the extrapyramidal side effects associated with the use of conventional neuroleptic agents. Since particularly dopamine D3 and D4 receptor subtypes are concentrated in the limbic system (Taubes, *Science* 265 (1994) 1034), which
- 10 controls cognition and emotion, compounds which interact with these receptors are useful in the treatment of cognitive disorders. Such disorders may be the cognitive deficits which are a significant component of the negative symptoms (social withdrawal and unresponsiveness) of schizophrenia. Other disorders involving memory impairment or attention deficit disorders can also be treated with some of the compounds of this invention that interact specifically with
- 15 dopamine D3 and/or D4 receptor subtypes. Accordingly, a broad embodiment of the invention is directed to a compounds of Formula 1



where

- 20 the 6-membered A ring may be optionally substituted with up to four groups independently selected from halogen, hydroxy, lower alkyl, or lower alkoxy;

Ar represents optionally substituted aryl or heteroaryl

Z represents carbon or nitrogen provided that

where Z is carbon, R<sub>11</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy, or phenyl optionally substituted with one or two groups selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and  
where Z is nitrogen, R<sub>11</sub> represents an electron pair;

5 R<sub>5</sub> is hydrogen or lower alkyl;

L is an integer of from 1-4;

m is an integer of from 2-5;

n is 0, or an integer of from 1-4;

R<sub>12</sub> and R<sub>13</sub> independently represent lower alkyl; or together may represent (CR<sub>x</sub>R<sub>y</sub>)<sub>s</sub> where s is

10 an integer of from 1-6 and R<sub>x</sub> and R<sub>y</sub> independently represent hydrogen or lower alkyl;

CR'R" represents a methylene group optionally substituted with lower alkyl; and

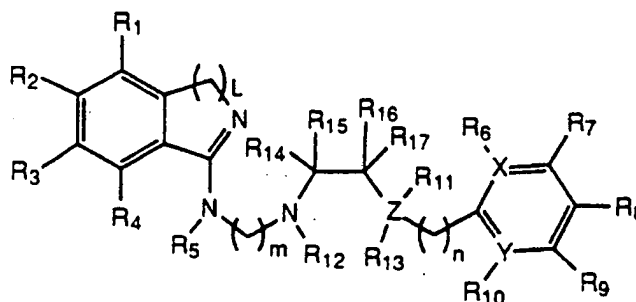
k is 0 or an integer of from 1 to 3.

Thus, the compounds of Formula 1 can be used in the treatment of various  
15 neuropsychochological disorders including, for example, schizophrenia, dementia, depression, anxiety, Parkinson-like motor disorders and motion disorders related to the use of neuroleptic agents.



DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general formula 1:



1a

wherein:

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

X represents carbon or nitrogen provided that

where X is carbon, R<sub>6</sub> represents hydrogen, halogen, hydroxy, lower alkyl having 1-6 carbon atoms, or lower alkoxy; and

where X is nitrogen, R<sub>6</sub> represents an electron pair;

Y represents carbon or nitrogen provided that

where Y is carbon, R<sub>10</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

where Y is nitrogen, R<sub>10</sub> represents an electron pair;

Z represents carbon or nitrogen provided that

where Z is carbon, R<sub>11</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy, or phenyl optionally substituted with one or two groups selected from hydrogen,

halogen, hydroxy, lower alkyl, or lower alkoxy; and

when Z is nitrogen, R<sub>11</sub> represents an electron pair;

R<sub>5</sub> is hydrogen or lower alkyl;

L is an integer of from 1-4;

m is an integer of from 2-5;

n is 0, or an integer of from 1-4;

R<sub>12</sub> and R<sub>13</sub> independently represent lower alkyl; or

R<sub>12</sub> and R<sub>13</sub> taken together may represent (CR<sub>x</sub>R<sub>y</sub>)<sub>s</sub> where s is an integer of from 1-6 and R<sub>x</sub> and

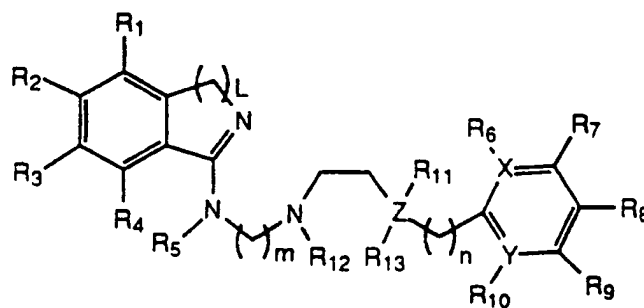
5 R<sub>y</sub> independently represent hydrogen or lower alkyl;

R<sub>7</sub> and R<sub>8</sub> together may represent a benzo ring optionally substituted with up to four substituents selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

R<sub>14</sub>, R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub> are the same or different and represent hydrogen or lower alkyl.

Preferred compounds of Formula 1a are those where s is an integer of from 1-4, and most  
10 preferably from 2-3.

The present invention also encompasses compounds of Formula 2:



2

15 wherein:

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

X represents carbon or nitrogen provided that

where X carbon, R<sub>6</sub> represents hydrogen, halogen, hydroxy, lower alkyl having 1-6  
20 carbon atoms, or lower alkoxy; and

where X is nitrogen, R<sub>6</sub> represents an electron pair.

Y represents carbon or nitrogen provided that

where Y is carbon, R<sub>10</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

where Y is nitrogen, R<sub>10</sub> represents an electron pair;

Z represents carbon or nitrogen provided that

- 5        where Z is carbon, R<sub>11</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy, or phenyl optionally substituted with one or two groups selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

when Z is nitrogen, R<sub>11</sub> represents an electron pair;

R<sub>5</sub> is hydrogen or lower alkyl;

- 10      L is an integer of from 1-4;

m is an integer of from 2-5;

n is 0, or an integer of from 1-4;

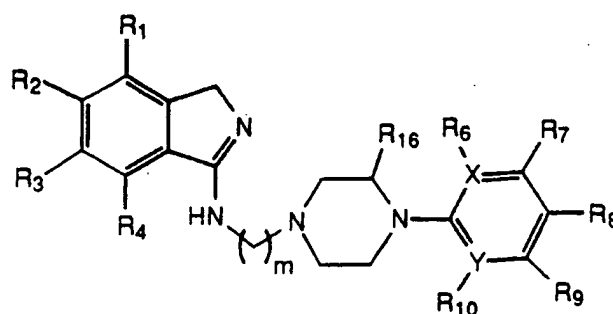
R<sub>12</sub> and R<sub>13</sub> independently represent lower alkyl; or

R<sub>12</sub> and R<sub>13</sub> taken together represent (CH<sub>2</sub>)<sub>s</sub> where s is an integer of from 1-6;

- 15      R<sub>7</sub> and R<sub>8</sub> together may represent a benzo ring optionally substituted with up to four substituents selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy.

Preferred compounds of Formula 2 are those where s is an integer of from 1-4, and most preferably from 2-3.

- 20        The present invention further encompasses compounds of Formula 3:



wherein:

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

R<sub>16</sub> represents hydrogen or lower alkyl;

5 X represents carbon or nitrogen provided that

where X carbon, R<sub>6</sub> represents hydrogen, halogen, hydroxy, lower alkyl having 1-6 carbon atoms, or lower alkoxy; and

where X is nitrogen, R<sub>6</sub> represents an electron pair;

Y represents carbon or nitrogen provided that

10 where Y is carbon, R<sub>10</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

where Y is nitrogen, R<sub>10</sub> represents an electron pair;

m is an integer of from 2-5;

R<sub>7</sub> and R<sub>8</sub> together optionally represent a benzo ring optionally substituted with up to four

15 substituents selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy.

Preferred compounds of formula 3 are those where m is 2, 3 or 4. Particularly preferred compounds of Formula 3 are those where m is 2 or 3; R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are hydrogen; R<sub>7</sub> and R<sub>9</sub>

are hydrogen and R<sub>8</sub> is hydrogen, hydroxy, halogen or alkoxy. More particularly preferred

compounds of Formula 3 are those where m is 2 or 3; R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are hydrogen; R<sub>16</sub> is

20 hydrogen or methyl; R<sub>7</sub> and R<sub>9</sub> are hydrogen; and R<sub>8</sub> is hydrogen, hydroxy or methoxy. Still

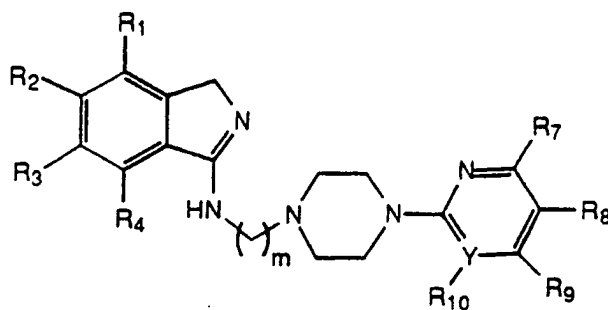
other preferred compounds of formula 3 are those where m is 2 or 3; X and Y independently

represent methylene optionally substituted with lower alkyl, preferably methyl; R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are

hydrogen; R<sub>16</sub> is hydrogen or methyl; R<sub>7</sub> and R<sub>9</sub> are hydrogen and R<sub>8</sub> is hydrogen, hydroxy or

methoxy.

The present invention also encompasses compounds of Formula 4:



4

wherein:

- 5 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

Y represents carbon or nitrogen provided that

where Y is carbon, R<sub>10</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

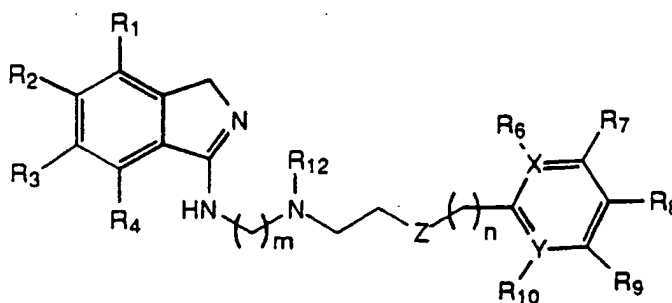
- 10 where Y is nitrogen, R<sub>10</sub> represents an electron pair;

m is an integer of from 2-5; and

R<sub>7</sub> and R<sub>8</sub> together may represent a benzo ring optionally substituted with up to four substituents selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy.

- Preferred compounds of formula 4 are those where m is 2, 3 or 4. Particularly preferred  
 15 compounds of Formula 4 are those where m is 2 or 3; and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are hydrogen; R<sub>7</sub> and R<sub>9</sub> are hydrogen; and R<sub>8</sub> is hydrogen, hydroxy, halogen or alkoxy. More particularly preferred compounds of Formula 4 are those where m is 2 or 3; and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are hydrogen; R<sub>7</sub> and R<sub>9</sub> are hydrogen; and R<sub>8</sub> is hydrogen, hydroxy or methoxy.

The present invention also encompasses compounds of Formula 5:



5

wherein:

- 5 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

X represents carbon or nitrogen provided that

where X carbon, R<sub>6</sub> represents hydrogen, halogen, hydroxy, lower alkyl having 1-6 carbon atoms, or lower alkoxy; and

- 10 where X is nitrogen, R<sub>6</sub> represents an electron pair;

Y represents carbon or nitrogen provided that

where Y is carbon, R<sub>10</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

where Y is nitrogen, R<sub>10</sub> represents an electron pair;

- 15 Z represents CH<sub>2</sub> or nitrogen;

m is an integer of from 2-5;

n is 0, or an integer of from 1-4;

R<sub>12</sub> represents hydrogen or lower alkyl; and

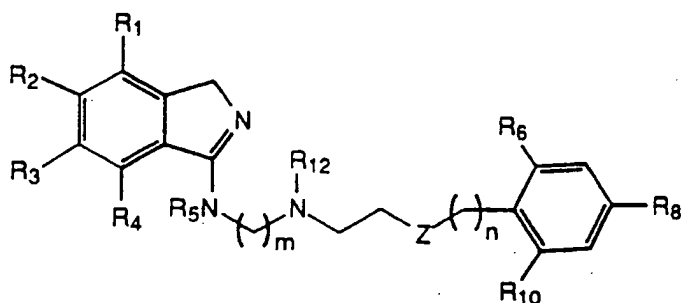
- 20 R<sub>7</sub> and R<sub>8</sub> together optionally represent a benzo ring optionally substituted with up to four substituents selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy.

Preferred compounds of formula 5 are those where m is 2, 3 or 4 and n is 0. Particularly preferred compounds of Formula 5 are those where R<sub>12</sub> is hydrogen or alkyl; m is 2, n is 0; Z is

CH<sub>2</sub>; R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are hydrogen; R<sub>7</sub> and R<sub>9</sub> are hydrogen; and R<sub>8</sub> is hydrogen, hydroxy, halogen or alkoxy. More particularly preferred compounds of Formula 5 are those where R<sub>12</sub> is hydrogen or methyl; m is 2; n is 0; Z is CH<sub>2</sub>; and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are hydrogen; R<sub>7</sub> and R<sub>9</sub> are hydrogen; and R<sub>8</sub> is hydrogen, hydroxy or methoxy.

5

In addition, the present invention provides compounds of Formula 6:



6

wherein:

- 10 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>8</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;
- R<sub>6</sub> and R<sub>10</sub> independently represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;
- Z represents CH<sub>2</sub> or nitrogen;
- m is an integer of from 2-5;
- 15 R<sub>5</sub> represents hydrogen or lower alkyl;
- n is 0, or an integer of from 1-4; and
- R<sub>12</sub> represents lower alkyl.

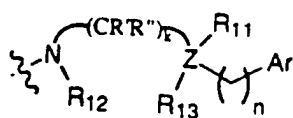
Preferred compounds of formula 6 are those where m is 2, 3 or 4 and n is 0. Particularly preferred compounds of Formula 6 are those where R<sub>12</sub> is hydrogen or alkyl; m is 2, n is 0; Z is CH<sub>2</sub>; R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are hydrogen; and R<sub>8</sub> is hydrogen, hydroxy, halogen or alkoxy. More particularly preferred compounds of Formula 6 are those where R<sub>12</sub> is hydrogen or methyl; R<sub>6</sub> is

20

hydrogen; R<sub>10</sub> is hydrogen or lower alkoxy, preferably methoxy; m is 2; n is 0; Z is CH<sub>2</sub>; and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> are hydrogen; and R<sub>8</sub> is hydrogen, hydroxy or methoxy.

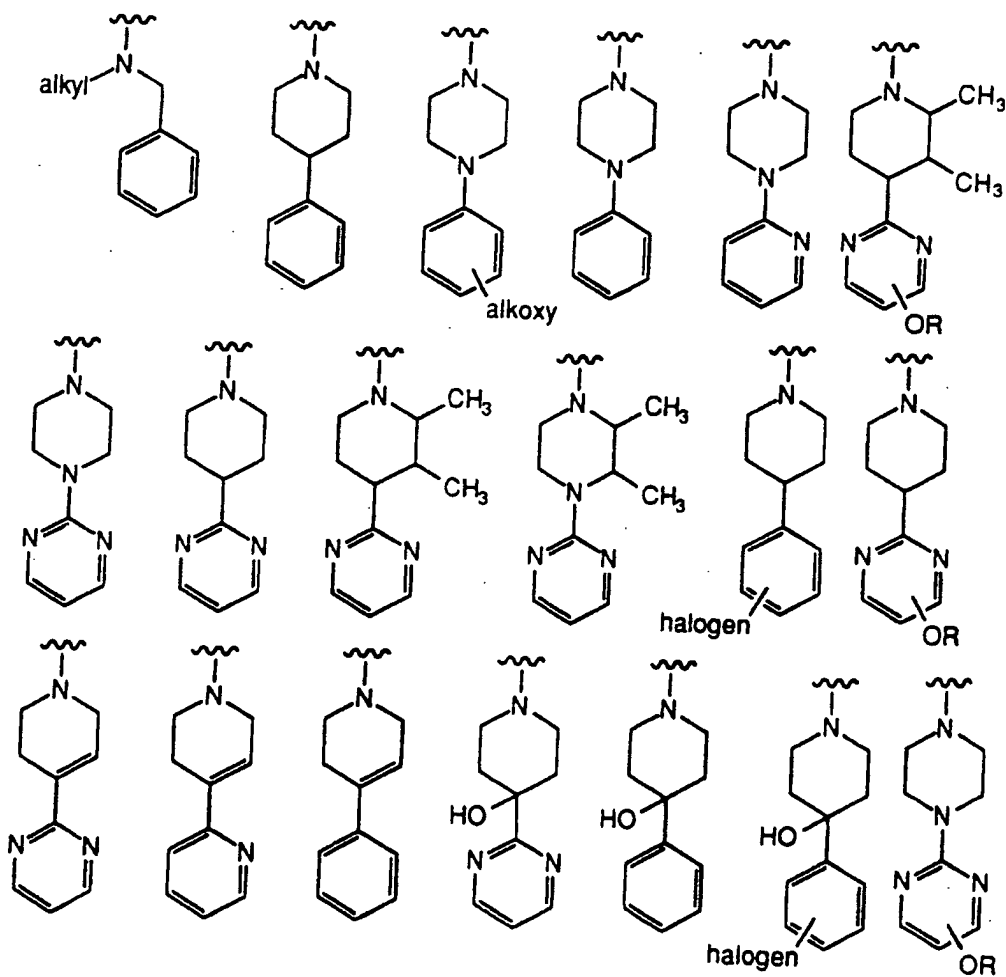
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Representative

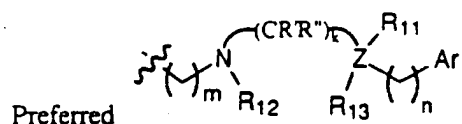


groups of formula 1 above include the

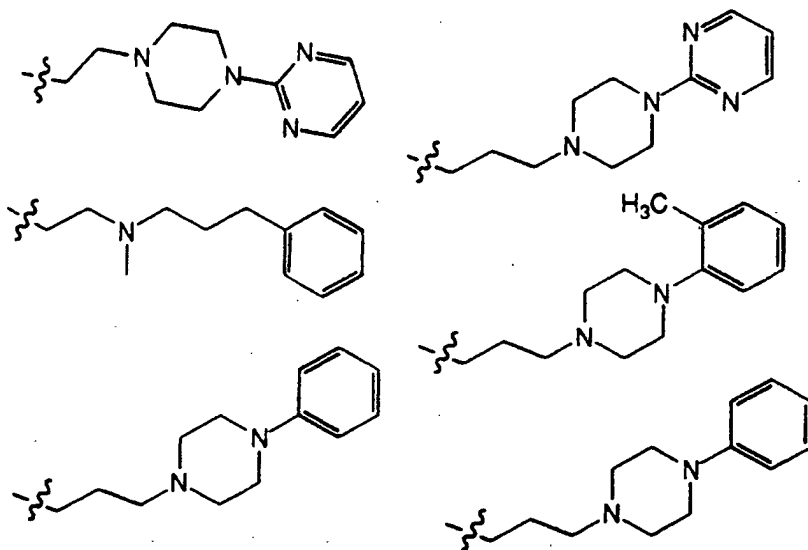
following:







groups of formula 1 above include the following:



In the above preferred groups, OR represents hydroxy or alkoxy.

Representative compounds of the present invention, which are encompassed by Formula 1, include, but are not limited to the compounds shown below in Table 1 and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluene sulfonic, hydroiodic, acetic and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of Formula 1. Those skilled in the art will recognize various synthetic methodologies which can be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula 1.

By "aryl" and "Ar" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic. (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which can

optionally be unsubstituted or substituted with e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy.

By "alkyl" and "lower alkyl" is meant straight and branched chain alkyl groups having from 1-6 carbon atoms.

5 By "lower alkoxy" and "alkoxy" is meant straight and branched chain alkoxy groups having from 1-6 carbon atoms.

By "heteroaryl" is meant 5, 6, or 7 membered aromatic ring systems having at least one hetero atom selected from the group consisting of nitrogen, oxygen and sulfur. Examples of heteroaryl groups are pyridyl, pyrimidinyl, pyrrolyl, pyrazolyl, pyrazinyl, pyridazinyl, oxazolyl, 10 furanyl, quinolinyl, isoquinolinyl, thiazolyl, and thienyl, which can optionally be unsubstituted or substituted with e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy.

By halogen is meant fluorine, chlorine, bromine and iodine.

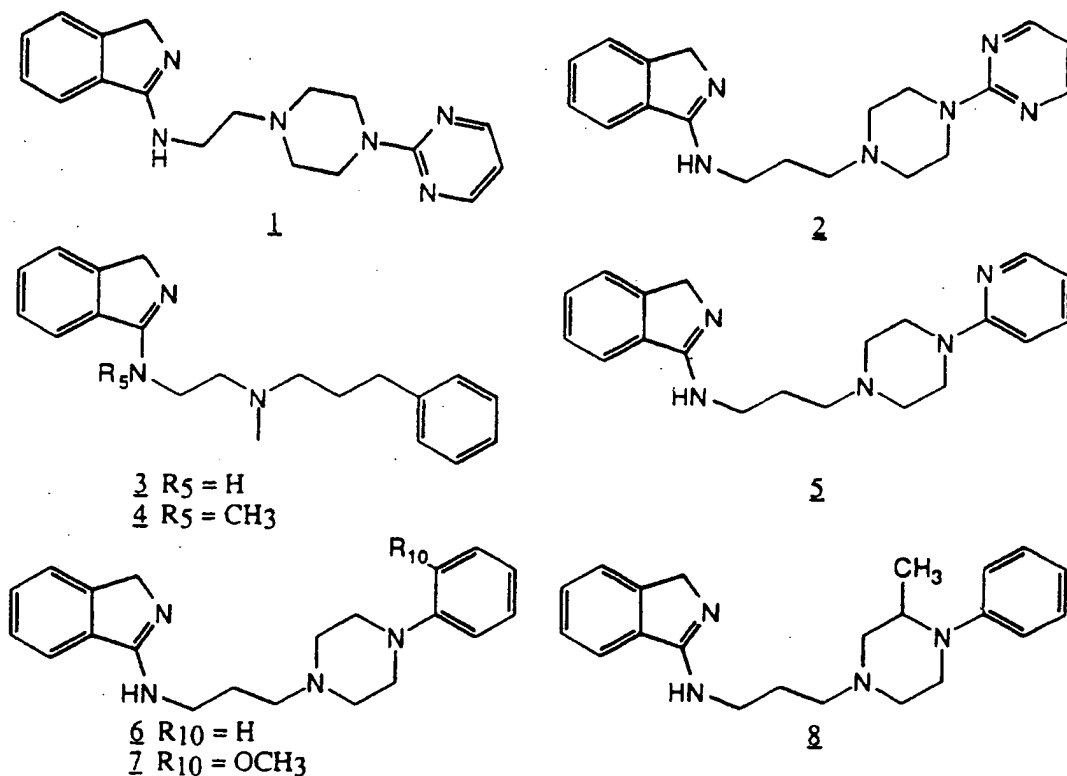
By alkylsulfonyl is meant a sulfonyl group substituted with a lower alkyl group.

15 By arylalkylsulfonyl is meant a sulfonyl group substituted with an arylalkyl group.

By aminosulfonyl is meant a sulfonyl group substituted with an amino group.

By alkylaminosulfonyl is meant a sulfonyl group substituted with a lower alkylamino, or di-lower alkylamino group.

Representative examples of bridged 4-phenyl-2-aminomethylimidazoles according to the 20 invention are shown in Table 1 below.

Table 1<sup>1</sup>

The number below each structure is its compound number.

The pharmaceutical utility of compounds of this invention are indicated by the following

5 assays for dopamine receptor subtype affinity.

#### Assay for D<sub>2</sub> and D<sub>3</sub> receptor binding activity

Pellets of COS cells containing recombinantly produced D<sub>2</sub> or D<sub>3</sub> receptors from African Green monkey were used for the assays. The sample is homogenized in 100 volumes (w/vol) of 0.05 M Tris HCl buffer at 4° C and pH 7.4. The sample is then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is then centrifuged as described and the final tissue sample is frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05 M Tris HCl buffer containing 100 mM NaCl.

Incubations are carried out at 48°C and contain 0.4 ml of tissue sample, 0.5 nM <sup>3</sup>H-YM 09151-2 and the compound of interest in a total incubation of 1.0 ml. Nonspecific binding is defined as that binding found in the presence of 1 mM spiperone; without further additions, nonspecific binding is less than 20% of total binding. The binding characteristics of examples of this patent for the D2 and D3 receptor subtypes are shown in Table 2 for Rat Striatal Homogenates.

**TABLE 2**

<u>Compound Number</u> <sup>1</sup>	<u>D<sub>2</sub> K<sub>i</sub> (mM)</u>	<u>D<sub>3</sub> K<sub>i</sub> (mM)</u>
<u>1</u>	2.380	>100
<u>2</u>	1.420	>100
<u>3</u>	1.937	>100

<sup>1</sup> Compound numbers relate to compounds shown in Table 1 above.

#### 10 Assay for D<sub>4</sub> receptor binding activity

Clonal cell lines expressing the human dopamine D<sub>4</sub> receptor subtype were harvested in PBS and the cells centrifuged and the pellets stored at -80° C until used in the binding assay. The pellets were resuspended and the cells lysed at 4° C in 50 mM Tris pH 7.4 buffer containing 120 mM NaCl, 1 mM EDTA and 5 mM MgCl<sub>2</sub>. The homogenate is centrifuged at 48000 x g for 10 minutes at 4° C. The resulting pellet is resuspended in fresh buffer and centrifuged again. After resuspension of the pellet in fresh buffer a 100 ml aliquot is removed for protein determination. The remaining homogenate is centrifuged as above, the supernatant removed and the pellet stored at 4° C until needed at which time it is resuspended to a final concentration of 625 mg/ml (250 mg per sample) with 50 mM Tris buffer (pH 7.4) and 120 mM NaCl just prior to use. Incubations were carried out for 60 minutes at 25° C in the presence of 0.1 nM [<sup>3</sup>H] YM-09151-2. The incubation was terminated by rapid filtration through Whatman GF/C filters and rinsed with 2 x 4 ml washes of chilled 50 mM Tris (pH 7.4) and 120 mM NaCl. Non-specific binding was determined with 1 mM spiperone and radioactivity determined by counting in an LKB beta counter.

Binding parameters were determined by non-linear least squares regression analysis, from which the inhibition constant  $K_i$  could be calculated for each test compound. The binding characteristics of some examples of this invention are shown in Table 3 for the dopamine D<sub>4</sub> binding assay. In general, compounds of the accompanying Examples were tested in the above assay, and all were found to possess a  $K_i$  value for the displacement of [<sup>3</sup>H]YM-09151-2 from the human dopamine D<sub>4</sub> receptor subtype of below 500 nM. Some specific data is indicated in Table 3.

**Table 3**

<u>Compound Number</u> <sup>1</sup>	<u><math>K_i</math> (nM)</u>
1	0.012
2	0.070
3	0.100

<sup>1</sup> Compound numbers relate to compounds shown in Table 1 above.

Compounds 1 and 2 are particularly preferred embodiments of the present invention because of their profile in binding to dopamine receptor subtypes.

The compounds of general Formulas 1 may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula 1 and a pharmaceutically acceptable carrier. One or more compounds of general Formula 1 may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula 1 may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan

monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, 5 for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

10 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

15 Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, 20 anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a 25 preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents

which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula 1 may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula 1 may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

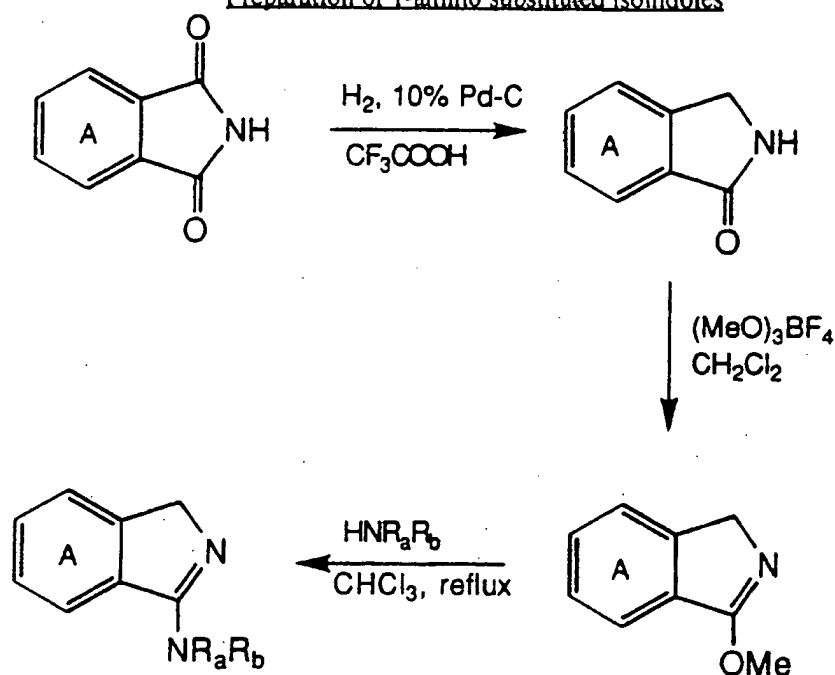


The compounds of the invention may be prepared by the reactions shown below in Scheme 1.

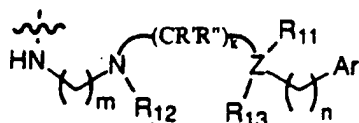
1. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce other compounds encompassed by the present invention.

**SCHEME 1**

5

Preparation of 1-amino substituted isoindoles

where the A ring is as defined above and  $\text{NR}_a\text{R}_b$  represents the group



wherein  $\text{CR}'\text{R}''$ ,  $k$ ,  $\text{R}_{11}$ ,  $\text{R}_{12}$ ,  $\text{R}_{13}$ ,  $\text{Ar}$ , and  $m$

and  $n$  are as defined above.

10

The invention is further illustrated by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described therein.

### Example 1

To a solution of trimethyloxonium tetrafluoroborate (2.20 g, 14.9 mmol) in (CH<sub>2</sub>Cl<sub>2</sub>, 20 mL) was added a solution of phthalimidine (1.8 g, 13.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and the solution was stirred for 24 h. The solvent was evaporated in vacuo and the residue was dissolved in chloroform (80 mL). To this solution was added 1-(aminoethyl)-4-(2-pyrimidinyl)piperazine (2.08 g, 9.0 mmol) followed by triethylamine (5 mL). The solution was boiled under reflux overnight and then the solvent was evaporated in vacuo to afford a semisolid residue. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (3 x 100 mL) to remove unreacted phthalimidine and primary amine. The aqueous solution was adjusted to about 20% NaOH by slow addition of aqueous 50% NaOH and then extracted with chloroform (2 x 100 mL). The combined chloroform extracts were dried (K<sub>2</sub>CO<sub>3</sub>) and evaporated to give Compound 1 as a pale yellow oil (2.9 g, quantitative). The hydrobromide salt was crystallized from hot ethanol. This compound had a melting point of 292-295°C (dec.).

### Example 2

To a solution of trimethyloxonium tetrafluoroborate (1.10 g, 7.45 mmol) in (CH<sub>2</sub>Cl<sub>2</sub>, 10 mL) was added a solution of phthalimidine (0.9 g, 6.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and the solution was stirred for 24 h. The solvent was evaporated in vacuo and the residue was dissolved in chloroform (40 mL). To this solution was added 3-(aminopropyl)-4-(2-pyrimidinyl)piperazine (1.1 g, 4.5 mmol) followed by triethylamine (5 mL). The solution was boiled under reflux overnight and then the solvent was evaporated in vacuo to afford a semisolid residue. The residue was dissolved in water (50 mL) and extracted with ethyl acetate (3 x 50 mL) to remove unreacted phthalimidine and primary amine. The aqueous solution was adjusted to about 20% NaOH by slow addition of aqueous 50% NaOH and then extracted with chloroform (2 x 50 mL). The combined chloroform extracts were dried (K<sub>2</sub>CO<sub>3</sub>) and evaporated to give Compound 2 as a pale yellow oil (0.75 g, 38%). The hydrobromide salt crystallized from hot ethanol: mp 149-150 °C;

base <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.38 (d, 2H), 7.3-7.5 (m, 5H), 6.55 (t, 1H), 4.62 (s, 2H), 3.9 (m, 4H), 3.63 (m, 2H), 2.63 (m, 6H), 1.8 (m, 2H).

### Example 3

5       The following compounds are prepared essentially according to the procedures set forth above in Examples 1 and 2.

(a) 1-(N-[2-(N'-(3-phenylpropyl)-N'-methyl)aminoethyl])aminoisindole dioxolate, Compound 3, m.p. 175-177°C.

(b) 1-(N-[2-(N'-(3-phenylpropyl)-N'-methyl)aminoethyl]-N-methyl])aminoisindole, 10 Compound 4.

(c) 1-(N-[3-{1-(4-(2-pyridyl)piperazinyl)}propylamino]) aminoisindole dihydrobromide, Compound 5, m.p. 283-285°C (dec.).

(d) 1-(N-[3-{1-(4-phenylpiperazinyl)}propyl])aminoisindole dihydrobromide, Compound 6, m.p. 208-211°C.

15 (e) 1-(N-[3-{1-(4-(2-methoxyphenyl))piperazinyl}propyl]) aminoisindole dihydrobromide, Compound 7, m.p. 184-185°C.

(f) 1-(N-[3-{1-(4-phenyl-3-methyl)piperazinyl}propyl]) aminoisindole dihydrobromide, Compound 8.

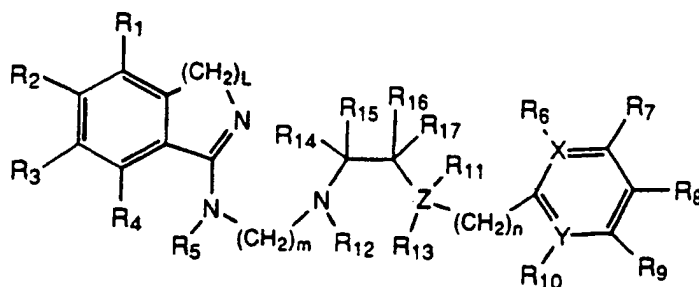
20       The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The invention and the manner and process of making and using it are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred 25 embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly

point out and distinctly claim the subject matter regarded as invention, the following claims conclude the specification.

What is claimed is:

1. A compound of the formula:



or the pharmaceutically acceptable salts thereof wherein:

- 5 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;
- X represents carbon or nitrogen provided that
- where X carbon, R<sub>6</sub> represents hydrogen, halogen, hydroxy, lower alkyl having 1-6 carbon atoms, or lower alkoxy; and
- 10 where X is nitrogen, R<sub>6</sub> represents an electron pair;
- Y represents carbon or nitrogen provided that
- where Y is carbon, R<sub>10</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and
- where Y is nitrogen, R<sub>10</sub> represents an electron pair;
- 15 Z represents carbon or nitrogen provided that
- where Z is carbon, R<sub>11</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy, or phenyl optionally substituted with one or two groups selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and
- when Z is nitrogen, R<sub>11</sub> represents an electron pair;
- 20 R<sub>5</sub> is hydrogen or lower alkyl;
- L is an integer of from 1-4;
- m is an integer of from 2-5;

n is 0, or an integer of from 1-4;

R<sub>12</sub> and R<sub>13</sub> independently represent lower alkyl; or

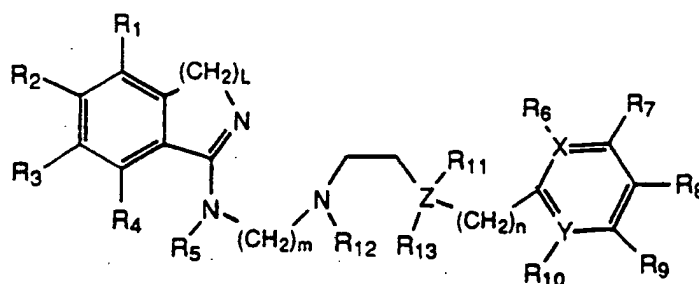
R<sub>12</sub> and R<sub>13</sub> taken together represent (CH<sub>2</sub>)<sub>s</sub> where s is an integer of from 1-6;

R<sub>7</sub> and R<sub>8</sub> together may represent a benzo ring optionally substituted with up to four substituents

5 selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

R<sub>14</sub>, R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub> are the same or different and represent hydrogen or lower alkyl.

2. A compound of the formula:



10 or the pharmaceutically acceptable salts thereof wherein:

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy;

X represents carbon or nitrogen provided that

where X carbon, R<sub>6</sub> represents hydrogen, halogen, hydroxy, lower alkyl having 1-6 carbon atoms, or lower alkoxy; and

where X is nitrogen, R<sub>6</sub> represents an electron pair;

Y represents carbon or nitrogen provided that

where Y is carbon, R<sub>10</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and

where Y is nitrogen, R<sub>10</sub> represents an electron pair;

Z represents carbon or nitrogen provided that

where Z is carbon, R<sub>11</sub> represents hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy, or phenyl optionally substituted with one or two groups selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy; and  
when Z is nitrogen, R<sub>11</sub> represents an electron pair;

5 R<sub>5</sub> is hydrogen or lower alkyl;

L is an integer of from 1-4;

m is an integer of from 2-5;

n is 0, or an integer of from 1-4;

R<sub>12</sub> and R<sub>13</sub> independently represent lower alkyl; or

10 R<sub>12</sub> and R<sub>13</sub> taken together represent (CH<sub>2</sub>)<sub>s</sub> where s is an integer of from 1-6;

R<sub>7</sub> and R<sub>8</sub> together may represent a benzo ring optionally substituted with up to four substituents selected from hydrogen, halogen, hydroxy, lower alkyl, or lower alkoxy.

3. A compound of Claim 1 which is 1-(N-[2-{1-(4-(2-  
15 pyrimidyl)piperazinyl)}ethyl])aminoisindole.

4. A compound of Claim 1 which is 1-(N-[3-{1-(4-(2-  
pyrimidyl)piperazinyl)}propylamino)amino)isindole.

20 5. A compound of Claim 1 which is 1-(N-[2-{N'-(3-phenylpropyl)-N'-  
methyl}aminoethyl])aminoisindole.

6. A compound of Claim 1 which is 1-(N-[2-{N'-(3-phenylpropyl)-N'-  
methyl}aminoethyl]-N-methyl])aminoisindole.

25

7. A compound of Claim 1 which is 1-(N-[3-{1-(4-(2-  
pyridyl)piperazinyl)}propylamino])aminoisindole.

8. A compound of Claim 1 which is 1-(N-[3-{1-(4-phenylpiperazinyl)}propyl])aminoisindole.

5 9. A compound of Claim 1 which is 1-(N-[3-{1-(4-(2-methoxyphenyl))piperazinyl}propyl])aminoisindole.

10. A compound of Claim 1 which is 1-(N-[3-{1-(4-phenyl-3-methyl)piperazinyl}propyl])aminoisindole.



# INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/US 97/00967

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D403/14 A61K31/505 C07D209/44 A61K31/40 C07D401/14  
A61K31/495 C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 39403 A (NEUROGEN CORPORATION) 12 December 1996 see the whole document ---	1-10
X	ARZNEIMITTEL FORSCHUNG DRUG RESEARCH, vol. 30, no. 9, 1980, pages 1487-1493, XP002010421 H.J.MAY ET AL: "Chemie und biologische Eigenschaften substituierter 3-Amino-1H-isoindole" see page 1489; example 18 -----	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

31 July 1997

Date of mailing of the international search report

1 5. 09. 97

Name and mailing address of the ISA

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Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
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Authorized officer

Gettins, M

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/00967

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1,2  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see annex
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

### Information on patent family members

Internal Application No

PCT/US 97/00967

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9639403 A	12-12-96	US 5602168 A	11-02-97
		AU 5982696 A	24-12-96
-----			